APJAI
Asian Pacific Journal of
Allergy and Immunology

ORIGINAL ARTICLE

Neuropsychiatric adverse effects of antihistamine: A nationwide data-based epidemiological study in South Korea

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Abstract

Background: Despite concerns on the major neuropsychiatric side effects for long-term use of H1-receptor antagonist (anti-histamine, AH), one of the major therapeutic tools for allergic diseases, their association has not been investigated well.

Objective: This study aimed to assess the association between AH usage and neuropsychiatric disorder (NPD) incidence using the National Health Insurance Service Database.

Methods: This study was conducted using data from the National Health Insurance Service Database from January 1st 2002 through December 31th 2017. To enroll the participants who may have history of long-term use of AH, participants having common allergic diseases were enrolled. We defined NPD as diagnosed by a psychiatrist occurring during and after antihistamine use to 6 months thereafter.

Results: A total of 1,488,075 participants were enrolled. No significant association was found between increased AH usage and NPD incidence after adjusting for potential confounding factors in the health screening data. Notably, the 30–89 day AH usage group showed a significantly lower NPD risk in the subgroup analysis in participants aged over 60 years. No other groups within this age category showed a significant increase in risk.

Conclusion: This study suggests that long-term AH use does not significantly increase NPD risk. While this study lacked evaluation of mild neuropsychiatric side effects not requiring psychiatric visits, this study may contribute real-world evidence to the understanding of AHs' long-term neuropsychiatric side effects.

Key words: Antihistamine, Psychiatric Disorders, Drug Side Effects, Health Insurance, Allergic Diseases

Citation:
Kim, J. Y., Kim, Z., Kim, S. H., Son, K. L., Rhee, C. S., Yoon, H. J. (0000). Neuropsychiatric adverse effects of antihistamine: A nationwide data-based epidemiological study in South Korea. *Asian Pac J Allergy Immunol*, 00(0), 000-000. https://doi.org/10.12932/ap-100724-1889

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Introduction

It is well-known that allergic diseases are one of the most widespread and common chronic diseases currently. According to World Allergy Organization (WAO),[1] the prevalence of allergic diseases has increased in the last decades with about 30–40% of the world population now being influenced by one or more allergic diseases. A typical feature for allergic diseases is chronicity and persistency which often require long-term medical treatment. In a previous study performed in Malaysia,[2] the prevalence of persistent allergic rhinitis was 68.9%, while that of intermittent allergic rhinitis was 31.1%. In addition, a large survey performed in Poland with 4783 patients with allergic rhinitis, found the rates of persistent and intermittent allergic rhinitis to be 52.3% and 47.7%, respectively.[3]

Histamine is a major inflammatory mediator for most allergic diseases, and H1-receptor antagonist (anti-histamine, AH) is one of the major arms for managing allergic diseases. Because of the chronicity and persistency of allergic diseases, long-term use of AH is often needed in patients with allergic diseases to control histamine-release related symptoms. There are two-generations of oral AHs: first- and second-generation AHs. First-generation AHs, such as chlorpheniramine, are related with central nervous system (CNS) side effects, which can cause neuropsychiatric disorder such as sedation and mental impairment.[4] Second-generation AHs has less CNS side effects and lower risk of drowsiness and sedation.[5] According to the Allergic Rhinitis and its Impact on Asthma (ARIA) guideline,[6] the second-generation AHs are the first-choice treatment for allergic rhinitis. Moreover, the second-generation AHs are the first- and second-choice (high-dose) treatment according to the EAACI/GA(2)LEN/EDF/WAO.[7]

Because of the neuropsychiatric side effect of AHs, the safety and tolerability of AHs are frequently considered when prescribing them for allergic diseases, and proper evidence for neuropsychiatric side effects of AHs should be investigated. Moreover, the evaluation period for neuropsychiatric side effects of AHs is mostly short and the neuropsychiatric side effects of long-term usage of AHs have not been properly evaluated.[8-14] In addition, a recent study based on Food and Drug Administration Adverse Event Reporting System (FAERS), was performed to evaluate the association between NPD and AHs; however, not all patients reported their neuropsychiatric side effects.[15] As Korean people are required to enroll in the national health insurance, individual AH usage and NPD history can be accessed via National Health Insurance Service Database, which may provide the evidence for association between NPD and AHs. This study thus aimed to evaluate the association between the usage of AHs and incidence of NPD based on the National Health Insurance Service Database.

Methods

Data source and study population

This retrospective cohort study was conducted using data from the National Health Insurance Service Database from January 1st 2002 through December 31th 2017. National Health Insurance Service (NHIS) covers all Korean citizens and Health screening is mandatory for all adults. Medical claim data for items being covered by NHIS are collected for billing purpose and anonymized data are provided. NHIS data includes diagnosis of diseases (International Classification of Diseases 10th revision; ICD–10), history of drug prescriptions, and health screening including physical measurements, laboratory test results, as well as questionnaire for family history, smoking, drinking, and physical activity.

To enroll the participants who may have history of long-term usage of AH, participants having five common allergic diseases including rhinitis (ICD–10, J30), conjunctivitis (H10), asthma (J45), allergic contact dermatitis (L23), and urticaria (L50) were enrolled. These allergic diseases were diagnosed based on their ICD-10 codes. Furthermore, to adjust potential confounding factors for the occurrence of NPD, participants who underwent at least one health screening between January 1st 2002 and December 31th 2017 and had data for general health status were enrolled. Among the approximately 23 million patients who underwent at least one health screening between January 1st 2002 and December 31th 2017 and had a history of being diagnosed with any of the above five common allergic diseases, we obtained a simple random sample of 1,999,984 participants (about two million participants).

Definition of outcome

We defined neuropsychiatric disorder (NPD) as having one or more of the following diseases diagnosed during January 1st 2004 to December 31th 2017, occurring during and after antihistamine use to 6 months thereafter: Cognitive disorder (F03, F05, F06.7, R41.8, G30.8), depression (F32.0, F32.1, F33.0, F33.1, F33.8, F33.9, F34.0, F34.8, F34.9, F38.0, F38.1, F38.8, F39), anxiety disorder (F40.0, F41.0 – F41.3, F41.8, F41.9), sleep disorder (F51.1, G47.8), impulse control disorder (F63.9), learning disorder (F81.9), agitation (G25, R451), attention deficit disorder (F90.0), irritability (R45.4), suicidal behavior disorder (R45.8), and hallucination (R44.0 – R44.3, R44.8). NPD diagnosis was restricted to diagnosis by a psychiatrist.

Definition of drug usage

Maximum usage of AHs was defined as the maximum consecutively prescribed days before NPD event or end of study period. If AHs were prescribed within 2 weeks from the end of the previous prescription, then it was considered as consecutive antihistamine usage. The generic names of AHs used in this study are as follows: chlorpheniramine, hydroxyzine, cetirizine, levocetirizine, loratadine, desloratadine, fexofenadine, ketotifen, and azelastine.

Statistical Analysis

Incidence rate was calculated as the number of NPD cases per unit of person–time, which is the total time the population is at risk of disease. The risk of NPD occurrence by maximum usage of AHs was analyzed using logistic regression model. Model was built with independent variables, selected based on contribution to overall model fit. Odds ratios (ORs) with 95% confidence intervals (CIs) for NPD incidence were adjusted for the following covariates: age; body mass index (BMI); systolic blood pressure (mmHg); diastolic blood pressure (mmHg); sex; smoking (duration / amount); drinking (frequency / amount); exercise frequency; and history of hypertension, stroke, heart disease, diabetes, and cancer.

As a main analysis, we identified the risk of NPD occurrence according to the duration of AH usage for all participants using logistic regression. Additional subgroup analysis was conducted by stratifying the study population into five allergic disease groups (rhinitis; conjunctivitis; asthma; allergic contact dermatitis; and urticaria) and age. All analysis was performed using SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina).

Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval for the study and waiver for need to obtain informed consent for this research was given by the Seoul National University Hospital institutional review board (IRB waiver number E-2203-003-1302).

Results

Among the 1,999,984 participants who underwent at least one health screening between January 1st 2002 and December 31th 2017 and had a history of being diagnosed with any of the five common allergic diseases (rhinitis, conjunctivitis, asthma, allergic contact dermatitis, and urticaria), participants with any history of NPD between January 1st 2002 and December 31th 2004 and who might have underlying NPD not due to the use of AH, were excluded (washout period). Participants who had never undertaken health screening between January 1st 2005 to December 31st 2010 (447,119 individuals) were excluded. Additionally, 5,686 individuals who had missing data in health screening records and 59,104 individuals who did not take AHs during the study period were also excluded. The final cohort included a total of 1,488,075 participants. **Figure 1** schematically illustrates the process of selecting participants for this study.

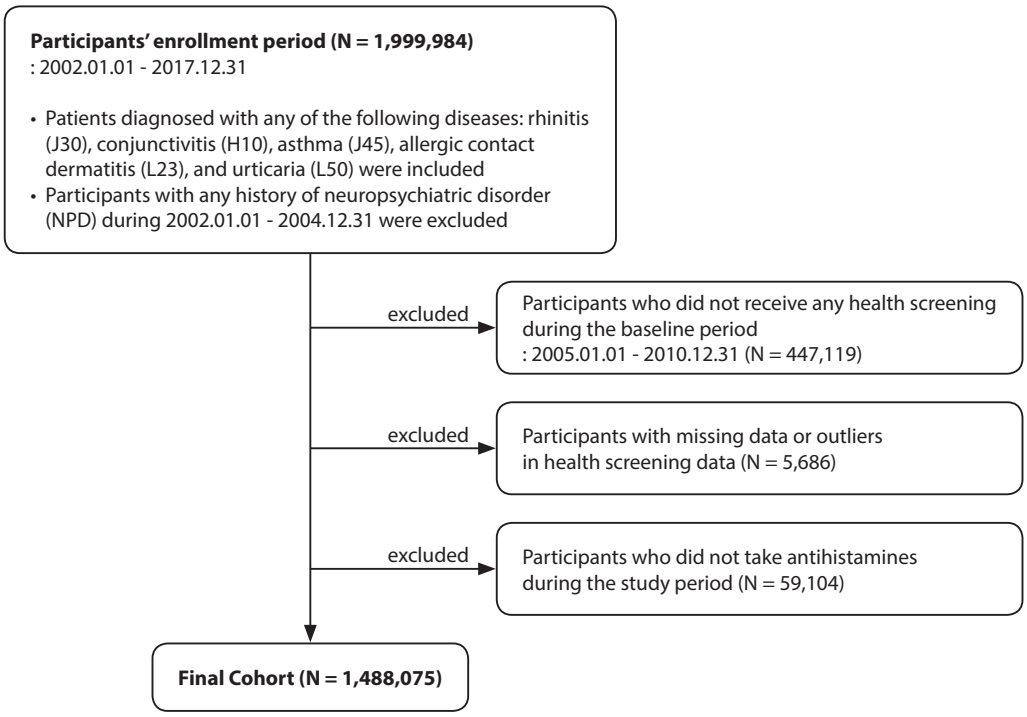

Figure 1. Enrollment and selection of the participants.

According to the maximum usage of AHs, participants were classified into five groups as follows: 1–6 days, 7–29 days, 30–89 days, 90–179 days, and 180 and more days of maximum consecutive usage of AHs (**Table 1**). Adjusted variables for the participants are shown in **Table 2**. Among the 1,488,075 participants, 7–29 days of maximum usage of AH accounted for the largest portion (%), and the number of participants decreased afterwards. Average age between each group gradually increased as the number of days of AH use increased (1–6 days: 40.31; 7–29 days: 43.41; 30–89 days: 47.85; 90–179 days: 49.42; 180 days and more: 51.77).

Table 3 shows the incidence rate between maximum usage of AHs and the risk of NPD after drug usage, stratified by maximum AH usage in 1–6, 7–29, 30–89, 90–179, and 180 or more days. There was no increase in risk of NPD according to the increase in maximum AH usage; moreover, no significant association between the maximum AH usage and NPD was found. In subgroup analysis with patients over 60 years of age (**Table 4**), the group of maximum AH usage, 30–89 days, showed significantly low OR of NPD (OR: 0.43, 95% CI: 0.02–0.94). No other groups within this age category exhibited a statistically significant increase in risk

Table 1. Demographics of the participants according to maximum antihistamine intake days.

	1–6 days N = 479,731 (32.24%)	7–29 days N = 855,361 (57.48%)	30–89 days N = 138,590 (9.31%)	90–179 days N = 12,799 (0.86%)	180+ days N = 1,594 (0.11%)	Total N = 1,488,075 (100%)
Antihistamine intake (day)	4.29 ± 1.30	12.68 ± 5.57	40.48 ± 13.53	102.52 ± 18.94	255.29 ± 179.44	13.60 ± 17.30
Age (y)	40.31 ± 12.80	43.41 ± 13.54	47.85 ± 13.97	49.42 ± 14.02	51.77 ± 14.07	42.89 ± 13.54
BMI (kg/m^2)	23.43 ± 3.21	23.54 ± 3.22	23.78 ± 3.20	23.81 ± 3.17	23.74 ± 3.31	23.53 ± 3.22
SBP (mmHg)	122.27 ± 15.84	122.16 ± 16.22	124.16 ± 16.97	124.77 ± 16.99	125.10 ± 16.86	122.41 ± 16.19
DBP (mmHg)	76.69 ± 10.76	76.51 ± 10.85	77.55 ± 11.08	77.92 ± 11.11	78.00 ± 11.15	76.68 ± 10.85
Sex Male	59.44%	48.85%	51.15%	55.23%	57.21%	52.54%
Female	40.56%	51.15%	48.85%	44.77%	42.79%	47.46%

180+ days indicates patients who took medication for more than 180 days.
BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure

Table 2. Baseline characteristics of the participants according to maximum antihistamine intake days during the study period.

		1–6 days N = 479,731 (32.24%)	7–29 days N = 855,361 (57.48%)	30–89 days N = 138,590 (9.31%)	90–179 days N = 12,799 (0.86%)	180+ days N = 1,594 (0.11%)	Total N = 1,488,075 (100%)
Smoking (duration) (year)	0	61.10%	69.74%	69.16%	67.47%	66.12%	66.88%
	< 5	4.12%	3.15%	2.50%	2.42%	1.94%	3.40%
	5~9	9.89%	6.44%	4.90%	4.47%	4.08%	7.39%
	10~19	14.52%	10.28%	9.24%	9.42%	8.85%	11.54%
	20~29	6.62%	5.87%	6.69%	6.95%	7.59%	6.20%
	≥30	3.75%	4.52%	7.51%	9.27%	11.42%	4.60%
Smoking (amount) (pack)	< 0.5	74.26%	81.83%	82.12%	81.85%	80.93%	79.42%
	0.5~1	18.02%	12.53%	12.01%	12.17%	12.80%	14.25%
	1~2	7.36%	5.32%	5.46%	5.52%	5.83%	5.99%
	≥2	0.36%	0.32%	0.41%	0.46%	0.44%	0.34%
Drinking (frequency) (times per week)	0	63.90%	69.71%	71.26%	71.72%	75.41%	68.00%
	1~2	25.35%	21.08%	18.66%	18.34%	16.19%	22.20%
	≥3	10.75%	9.21%	10.08%	9.94%	8.41%	9.80%
Drinking (amount) (bottles of soju)	< 0.5	62.16%	70.02%	73.10%	74.25%	77.48%	67.82%
	≥0.5	37.84%	29.98%	26.90%	25.75%	22.52%	32.18%

Table 2. (Continued)

		1–6 days N = 479,731 (32.24%)	7–29 days N = 855,361 (57.48%)	30–89 days N = 138,590 (9.31%)	90–179 days N = 12,799 (0.86%)	180+ days N = 1,594 (0.11%)	Total N = 1,488,075 (100%)
Exercise frequency (times per week)	0	51.51%	53.36%	54.21%	53.47%	56.84%	52.85%
	1~2	26.65%	24.44%	23.01%	22.63%	19.64%	25.00%
	≥3	21.84%	22.20%	22.78%	23.90%	23.53%	22.15%
Past HTN		5.63%	7.98%	12.25%	13.38%	14.12%	7.68%
Past STK		0.42%	0.51%	0.72%	0.92%	0.88%	0.50%
Past HTDZ		0.75%	1.12%	1.71%	2.21%	2.89%	1.07%
Past DM		2.38%	3.28%	5.22%	5.81%	6.27%	3.20%
Past CC		0.45%	0.59%	0.69%	0.77%	1.07%	0.55%

180+ days indicates patients who took medication for more than 180 days.
Value for variables is presented as the proportion of a group with a particular condition.
*HTN: Hypertension; STK: Stroke; HTDZ: Heart disease; DM: Diabetes; CC: Cancer

Table 3. Association between antihistamine use (maximum intake days during the study period) and the risk of neuropsychiatric disorder, occurring during and after antihistamine use to 6 months thereafter.

Antihistamine use days	N	NPD events (during 6 months right after drug usage)	Incidence Rate per 100,000 person–year	Adjusted OR (95% CI)	Corresponding *P*-value
Whole group (N = 1,488,075)					
1–6 days	479,731	123	1.83	1.00	.
7–29 days	855,361	184	1.54	0.79 (0.49-1.27)	0.3351
30–89 days	138,590	39	2.01	0.89 (0.53-1.50)	0.6706
90–179 days	12,799	3	1.67	0.72 (0.27-1.95)	0.5216
180+ days	1,594	1	4.48	1.81 (0.37-8.85)	0.4645

180+ days indicates patients who took medication for more than 180 days.
Bold text with * indicates statistical significance at 0.05 level.
OR was adjusted for age; body mass index; systolic blood pressure (mmHg); diastolic blood pressure (mmHg); sex; smoking (duration / amount); drinking (frequency / amount); exercise frequency; and history of hypertension, stroke, heart disease, diabetes, and cancer.
NPD, neuropsychiatric disorder; OR, odds ratio; CI, confidence interval

Table 4. Association between antihistamine use (maximum intake days during the study period) and the risk of NPD, occurred during and after antihistamine use to 6 month thereafter.

Antihistamine use days	N	NPD events (during 6 months right after drug usage)	Incidence Rate per 100,000 person–year	Adjusted OR (95% CI)	Corresponding *P*-value
Patients over 60 years of age (N = 203,992)					
1–6 days	44,449	19	3.05	1.00	.
7–29 days	122,550	36	2.10	0.60 (0.34-1.07)	0.0859
30–89 days	32,807	7	1.52	***0.43* (0.20-0.94)***	0.0341
90–179 days	3,629	2	3.94	1.15 (0.35-3.79)	0.8190
180+ days	557	1	12.83	3.75 (0.75-18.73)	0.1067

180+ days indicates patients who took medication for more than 180 days.
Bold text with * indicates statistical significance at 0.05 level.
OR was adjusted for age; body mass index; systolic blood pressure (mmHg); diastolic blood pressure (mmHg); sex; smoking (duration / amount); drinking (frequency / amount); exercise frequency; and history of hypertension, stroke, heart disease, diabetes, and cancer.
NPD, neuropsychiatric disorder; OR, odds ratio; CI, confidence interval

(Maximum AH usage 7–29 days, OR: 0.60, 95% CI: 0.34–1.07; 90–179 days, OR: 1.15, 95% CI: 0.35–3.79; 180 days and more, OR: 3.75, 95% CI: 0.75–18.73). Subgroup analysis based on the etiology was performed (**Supplementary Table 1**): history of rhinitis, conjunctivitis, asthma, allergic contact dermatitis, and urticaria. There was no significant increase according to the maximum usage of AHs.

Discussion

AHs are one of the most prescribed medications for allergic diseases. However, the neuropsychiatric side effects of AHs raise special concerns for the use of AHs. Although the short-term neuropsychiatric side effects of AHs have been investigated in several studies,[9-14] the evidence for long-term safety and tolerability of AHs was limited. Lack of evidence for the long-term safety and tolerability of AH commonly occurs in hospital data because controlled study for long periods is difficult for these patients. Therefore, the patients who have NPD during or after having AH do not always report their NPD to the clinician who have prescribed AHs; rather, they directly go to a psychiatrist. To overcome this problem, we determined to use the NHIS database. As NHIS database include all claims including psychiatric clinics, the NPDs associated with prescribed AHs could be found through it.

In this study, the incidence of NPD associated with AHs was investigated through the NHIS database. Among the 1,999,984 participants who had history of being diagnosed with any of the five common allergic diseases (rhinitis, conjunctivitis, asthma, allergic contact dermatitis, and urticaria), the incidence of NPD was evaluated according to the maximum usage of AH, after adjusting for clinical parameters from health screening. In contrast to the stereotype that the long-term use of AHs may increase neuropsychiatric side effects, the incidence of NPD associated with the use of AHs was not increased, according to the maximum consecutive usage of AHs. Rather, the OR of NPD was significantly low in the groups of maximum AH usage, 30–89 days, in the subgroup analysis of patients over 60 years of age. Considering that allergic diseases frequently require long-term medication use, we speculated that some participants who had the maximum AH usage, 1–6 days, might have more chance of developing neuropsychiatric side effects and seek other allergy medications. Moreover, patients over 60 years of age might have more experience about usage of allergy medications compared to that of the younger patients. Therefore, the group of maximum AH usage, 30–89 days, who might be tolerable to AHs, had significantly low incidence of NPDs in patients over 60 years of age. Although significance was not met, group of maximum AH usage, 180 days and more, tended to have high incidence of NPDs. Because there was only one NPD event that occurred, it was not certain whether the group of maximum AH usage, 180 days and more, had higher risk of NPD than that of the group of maximum AH usage, 1–6 days, in patients over 60 years of age. However, the changes in OR according to the maximum AH usage (1 -> 0.60 -> 0.43 -> 1.15 -> 3.75) may indicate that long-term AH usage may increase the risk of NPD in old age.

Neuropsychiatric adverse effects can pose a significant challenge when treating allergic diseases. However, clinicians must be prepared to manage both conditions concurrently. For mild NPDs, reducing the AH dosage or switching to an AH with lower blood-brain barrier permeability should be considered.[16] In cases of severe NPD, in addition to these measures, referral to a consultation-liaison psychiatry department is recommended for the administration of psychotropic medications, such as antipsychotics, antidepressants, or anxiolytics, depending on the symptoms presented.[16]

This study has some limitations. First, the mild neuropsychiatric side effects to AHs that did not cause visits to psychiatrists were not evaluated. Participants who had undergone mild neuropsychiatric side effects that did not require psychiatric management might be reluctant to have AHs; the participants who had the maximum AH usage, 1–6 days, might have more chance of mild neuropsychiatric side effects. Second, the NPD history before 2002 was not evaluated; we excluded the participants who had any history of NPD (2002–2004) before the evaluation period (2005–2017). Lastly, although patients with allergy are commonly managed through clinics, some might prefer self-treatment by purchasing generic medications in pharmacies that is not covered by the NHIS. Despite these limitations, to the best of our knowledge, this is the first study to evaluate the long-term neuropsychiatric side effects based on national healthcare insurance database. In contrast to the hospital-based study, in which some participants could have medications from other hospital or clinics, NHIS-based study can cover all clinics and hospitals in Korea and minimize unrecorded medications.

"Given the limitations encountered in analyzing the effects of first-generation antihistamines due to the small number of long-term users in this study (90 days or more: all antihistamines, 4,186 versus first-generation antihistamines, 1,046 in patients over 60 years of age, data not shown), further research with a different study design is necessary. Notably, only one NPD case was detected throughout the study period (not limited to the 6-month follow-up) in the 1,046 patients who had used first-generation antihistamines for 90 days or more. For this reason, estimation of effect of first-generation antihistamine was not possible resulting in a wide confidence interval (0.00 to ∞) in patients over 60 years of age suggesting insufficient statistical power. Our logistic regression model demonstrated a wide confidence interval (0.00 to ∞) in patients over 60 years of age (data not shown), suggesting insufficient statistical power to draw meaningful conclusions about the impact of first-generation antihistamines on the development of NPD. Future studies with different study designs are necessary to investigate the effects of first-generation antihistamines on NPD."

Leukotriene antagonist is also commonly used in allergic diseases, and some previous studies showed the association between leukotriene antagonist and neuropsychiatric symptoms.[17-19] Therefore, usage of leukotriene antagonist might be a confounding factor. However, it is practically challenging to exclude all medications potentially associated with neuropsychiatric symptoms from the study. As the participants were extracted from the National Health Insurance Service Database, they may have various comorbidities beyond allergic diseases, making it difficult to exclude all medications potentially associated with neuropsychiatric symptoms. Furthermore, according to recent studies, there is no clear evidence proving the association of leukotriene antagonist with such symptoms.[20,21]

In conclusion, long-term use of AH did not significantly increase the NPD incidence in this NHIS-based study. Although the effect of mild neuropsychiatric side effects that does not need visit to psychiatric clinics was not evaluated, we believe that this study may enhance the evidence of long-term neuropsychiatric side effects of AH in the real world.

Acknowledgement

Not applicable

Funding

- This study was supported by a grant from the National Research Foundation of Korea (NRF-2021R1I1A1A010 56576), South Korea and by the Dongguk University, College of Medicine Research Fund of 2024.
- This work was supported by the Institute of Information & Communications Technology Planning & Evaluation (IITP)-Global Data-X Leader HRD program grant funded by the Korea government (MSIT) (IITP-2024-RS-2024-00 441407).

Statements and Declarations

The authors have no conflicts of interest to declare or any source of funding related to this study.

Data availability statement

The data used in this study is accessible from NHIS, with restrictions on public availability. However, access can be granted upon reasonable request and with IRB approval.

Author contributions

- Jin Youp Kim: Conceptualization, Methodology, Investigation, Writing – Original draft preparation;
- Zio Kim: Conceptualization, Methodology, Data curation, Formal Analysis, Software, Writing – Original draft preparation;
- Su Hwan Kim: Conceptualization, Methodology, Investigation, Data curation, Formal Analysis, Writing – Original draft preparation;
- Kyung-Lak Son: Writing – Reviewing and Editing;
- Chae-Seo Rhee: Supervision;
- Hyung-Jin Yoon: Supervision.

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Supplementary Table 1. Association between antihistamine use (maximum intake days during the study period) and the risk of NPD, occurring during and after antihistamine use to 6 months thereafter, stratified by etiology.

Antihistamine use days	N	NPD events (during 6 month right after drug usage)	Incidence Rate per 100,000 person–year	Odds Ratio (95% CI)	Corresponding *P*-value
Rhinitis (N = 1,442,011)					
1–6 days	451,875	122	1.93	1.00	
7–29 days	838,919	182	1.55	0.79 (0.49-1.26)	0.3178
30–89 days	136,936	39	2.03	0.89 (0.53-1.49)	0.6466
90–179 days	12,703	3	1.69	0.71 (0.26-1.92)	0.5028
180+ days	1,578	1	4.53	1.79 (0.37-8.76)	0.4722
Conjunctivitis (N = 1,187,654)					
1–6 days	343,249	103	2.14	1.00	
7–29 days	711,224	169	1.70	6.72 (0.00-∞)	0.9637
30–89 days	120,544	33	1.96	6.71 (0.00-∞)	0.9637
90–179 days	11,251	3	1.90	6.32 (0.00-∞)	0.9649
180+ days	1,386	0	0.00	0.00 (0.00-∞)	0.9623
Asthma (N = 803,729)					
1–6 days	185,008	72	2.78	1.00	
7–29 days	510,190	145	2.03	0.78 (0.48-1.26)	0.3067
30–89 days	97,488	33	2.42	0.82 (0.48-1.40)	0.4763
90–179 days	9,830	3	2.18	0.73 (0.27-1.97)	0.5347
180+ days	1,213	1	5.89	1.85 (0.38-9.05)	0.4486
Allergic contact dermatitis (N =1,167,219)					
1–6 days	318,654	112	2.51	1.00	
7–29 days	711,793	170	1.71	8.34 (0.00-∞)	0.9735
30–89 days	123,771	36	2.08	8.89 (0.00-∞)	0.9727
90–179 days	11,575	2	1.23	5.16 (0.00-∞)	0.9795
180+ days	1,426	0	0.00	0.00 (0.00-∞)	0.9732
Urticaria (N = 962,415)					
1–6 days	242,672	89	2.62	1.00	
7–29 days	595,068	151	1.81	0.83 (0.50-1.37)	0.4549
30–89 days	112,500	38	2.41	0.95 (0.55-1.64)	0.8546
90–179 days	10,802	2	1.32	0.51 (0.16-1.67)	0.2662
180+ days	1,373	1	5.20	1.86 (0.38-9.17)	0.4464

180+ days indicates patients who took medication for more than 180 days.
The number of patients is not mutually exclusive.
Bold text with * indicates statistical significance at 0.05 level.
OR was adjusted for age; body mass index; systolic blood pressure (mmHg); diastolic blood pressure (mmHg); sex; smoking (duration / amount); drinking (frequency / amount); exercise frequency; and history of hypertension, stroke, heart disease, diabetes, and cancer.
In the groups with history of conjunctivitis or allergic contact dermatitis, upper limit of 95% confidential intervals were not estimated due to the large value of standard error in these groups.
NPD, neuropsychiatric disorder; OR, odds ratio; CI, confidence interval